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The Effect of Medicinal Plants on Inflammatory Markers in HIV Patien-ts

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ABSTRACT

Despite the significant global progress in HIV management through antiretroviral therapy (ART), chronic immune activation and systemic inflammation persist in people living with HIV (PLWH), contributing to accelerated disease progression and comorbidities. In many low- and middle-income countries (LMICs), limited access to ART has led to the widespread use of traditional medicinal plants as complementary therapy. This study investigates the immunomodulatory potential of three medicinal plants—*Azadirachta indica* (Neem), *Moringa oleifera*, and *Momordica foetida*—commonly used by HIV-positive patients in Uganda. Using ethanol-water crude extracts, the study evaluated cytotoxicity, effects on CD4+ T cell activation/exhaustion markers, and modulation of key inflammatory cytokines (IL-6, TNF-α, IFN-γ, and hsCRP) in HIV-infected peripheral blood mononuclear cells (PBMCs). Results indicated that *A. indica* significantly reduced the expression of activation (CD69, CD38) and exhaustion (PD-1, CD127) markers, with a corresponding decrease in pro-inflammatory cytokines. The findings suggest that certain plant-derived compounds can potentially complement ART by mitigating immune dysregulation and systemic inflammation in HIV patients. This research underscores the need for further clinical validation and cautious integration of traditional herbal medicine in HIV care protocols.

Keywords: HIV/AIDS, Medicinal Plants, Chronic Immune Activation, Inflammatory Biomarkers, *Azadirachta indica*, CD4+ T Cell Exhaustion, Antiretroviral Therapy (ART).

INTRODUCTION

The Human Immunodeficiency Virus (HIV) chronically infects 38 million people worldwide. Despite the notable progress made in the creation of life-prolonging antiretroviral therapy (ART), the target of 90-90-90 has not been achieved globally, with only 73% of people living with HIV (PLWH) on treatment as of 2020 [1-4]. There has been sub-optimal funding for health systems in resource-limited settings, reflected in the ongoing lack of access to ART by over 60% of PLWH. As a consequence, HIV continues to be a major cause of morbidity/mortality in most low and middle-income countries (LMICs). Furthermore, there were 1.5 million new HIV infections and 679,000 AIDS-related deaths in 2020. In these settings, cultural differences and poor health care force the majority of PLWH to resort to traditional herbal therapy for alternative and/or complementary treatment [5-7]. Indeed, a survey in Kenya revealed that approximately 90% of actively ART-enrolled PLWH concurrently used traditional herbal medicines [8-9]. Hence, it is common for PLWH who are actively enrolled on ART to concurrently use traditional herbal medicines. This warrants the need for studies investigating any immune-boosting benefits arising from the routine use of medicinal plants for HIV diseases [10-12]. In HIV, the virus principally infects gut-homing CD4+ T cells and skews diverse cellular pathways to favour its replication. However, this is accompanied by a near-complete depletion of the memory central

and effector CD4+ T cell subsets from the gut [13-17]. This gut trojan horse phenomenon is coupled with the persistent activation and exhaustion of circulating CD4+ T cells as denoted by increased surface expression of (1) the early activation marker CD69, (2) the antigen-presenting molecule Human Leukocyte Antigen – DR (HLA-DR), (3) the metabolite marker CD38 [18-20]. Chronic T cell activation is mainly driven by continuous responses to bacterial antigens arising from gut microbial translocation. Early in infection, HIV causes irreparable damage to the gut epithelium. This causes gut microbes and bacterial products to traverse the gut protective barrier. This sets the stage for the establishment of systemic immune activation and subsequent HIV pathogenesis. Chronic T cell activation has been linked to accelerated progression to AIDS. Among HIV infected individuals, chronic immune activation is suggested as a better predictor of AIDS events compared to viral load and CD4+ T cell count [21-25].

Background on HIV and Inflammation

HIV creates an imbalance between infectiousness and the immune response, leading to acquired immunodeficiency syndrome (AIDS). Antiretroviral therapy (ART) reduces HIV replication, viral load, and associated disabilities, achieving undetectable levels and preventing transmission. However, ART does not eliminate HIV or restore normal immunity, leaving individuals with HIV (PWH) at a higher risk for pneumonia, neurocognitive and cardiovascular disorders, malignancies, and other diseases. The persistence of HIV despite ART is linked to cellular sanctuaries [26-29]. Research indicates that measuring HIV markers during ART can signal treatment failure or progression in untreated cases, yet no ART factor has been shown to decrease inflammatory disease risk in treated individuals. ART normalizes various immune system features within 2 to 8 months, but doesn't fully address systemic immune activation. Future research on aging, inflammation, ART, and cardiovascular risks should clarify causal relationships and the impact of systemic inflammation on cardiovascular disease mechanisms. Furthermore, milder complications from ART require evaluation for enhanced risk–benefit models in HIV treatment [30-34]. Addressing aging effects through optimized clinical studies can unveil the complexities of immune responses. While ART improves longevity and health for PWH, it does not resolve HIV disease, necessitating strategies targeting latent infection, immune dysregulation, inflammation, and aging. The timing and combination of these strategies need exploration. Additionally, caution is warranted when drawing comparisons in trial outcomes between varied risk profiles from different regions, ensuring careful evaluation of international health proposals [35-38].

Overview of Medicinal Plants

The present study aimed to investigate the in vitro immunomodulatory activity of selected medicinal plants used by people living with HIV in Uganda. Ethanol: water mixtures of three plant species: Moringa oleifera (leaves), Azadirachta indica (leaves), and Momordica foetida (seeds) were prepared and their toxicity evaluated using the MTT cell viability assay [39-40]. HIV-infected Peripheral Blood Mononuclear Cells (PBMCs) were activated with Staphylococcus aureus enterotoxin B, treated with the plants, and assessed for expression of co-stimulatory, exhaustion, and cytokine markers using flow cytometry and ELISPOT. It was found that only the A. indica leaf ethanol: water mixture was non-toxic to PBMCs. Treatment of activated PBMCs with the A. indica leaf ethanol: water mixture induced a significant reduction in the expression of activation and exhaustion markers: CD69, CD38, PD-1, and CD127 compared to the DMSO-treated control. A subsequent ELISPOT assay detected a similar decrement in the production of viral suppression cytokine: Interferon gamma. This study provides a comprehensive treatment modality in which DM and ART can be combined to achieve improved clinical outcomes of ART. It was concluded that treatment with the A. indica leaf ethanol: water mixture can down-regulate activation and exhaustion markers on HIV infected CD4+ T-cells. Human Immunodeficiency Virus (HIV) is a lentivirus of the retroviridae family that deleteriously affects T cells of the immune system. HIV-1 specifically employs the chemokine receptors and entry cofactors CCR5 and CXCR4 on the target CD4+ T cells to gain entry into the host cell. The switching of co-receptors by HIV-1 or cellular tropism is not only responsible for disease progression but also a crucial parameter in selecting the most optimal therapeutic agent, implicit in stem cell transplantations. It was also noticed that cellular tropism is implicated in the neuropathogenesis of HIV, along with the mechanisms of HIV transmission and infection, and the epidemiological studies. These findings underscore the importance of understanding the switching of co-receptors and the relationship between the switching of co-receptors and target cell tropism in developing an optimal therapeutic agent [6].

Mechanisms of Inflammation in HIV

Infection by the human immunodeficiency virus (HIV) and consequent development of acquired immunodeficiency syndrome (AIDS) taken in combination significantly increase inflammatory markers that are implicated in a nexus of diseases, each with a significant risk of mortality. HIV infection is associated with a 2-3-fold increased risk of adverse health outcomes often observed in aging populations, such as vascular, liver, renal, and neurodegenerative diseases with their associated morbidity [38-43]. Despite large improvements in the treatment of individual HIV infection and recapitulation of lifespan expectations with antiretroviral therapy (ART), the risk of a Hampton Roads decline remains greater than uninfected individuals with similar age and cardiovascular risk profiles. Several mechanisms for increased inflammation and consequent disease processes have been put forward. Viable HIV within the viral reservoir remains compartmentalized and unquantifiable due to the existence of post-ART treatment failure. Further studies are ongoing to determine the mechanism of inflammation and the associated persistence of residual systemic immune activation following chronic effective ART. While the introduction of ART soon after acute HIV infection is the best means to limit inflammation and its pathological consequences, people frequently become infected with HIV, particularly in developing regions of the world [44-47]. Hence, less practical epidemiologic and biobehavioral approaches to limit infection and reduce risk of transmission and acquisition are currently being evaluated. These principally concern behavioral modulations, both pharmaceutical and social in nature, to lower viral shedding from infected people and susceptibility to infection in at-risk individuals. Another face of prevention recently gaining attention is hosting systems of dietary micronutrients and phytochemicals. Effects on inflammation in HIV of orally ingested medicinal plants are critically discussed, outlining the scientific rationale and the relevant phytochemicals and their pro- and anti-oxidative chemical activity [8].

Role of Medicinal Plants in Traditional Medicine

Medicinal plants have been used for therapeutic purposes for centuries. A great variety of plants have been used to augment the immune system, detoxify the body, or reduce the effects of HIV/AIDS. For the majority of patients in resource-limited settings, herbal medicine is used as first-line therapy. This, combined with the frequent and widespread use of anti-retroviral drugs such as efavirenz and nevirapine, has raised concern that patients may experience herb-drug interactions due to the induction and/or inhibition of cytochrome P450 enzymes. Plants have the potential for both effects as they contain a large variety of bioactive compounds. CYP2B6 is the main cytochrome P450 enzyme involved in the metabolism of the non-nucleoside reverse transcriptase inhibitors. High levels of circulating efavirenz are associated with severe toxicity events, and this has prompted the investigation of CYP2B6 polymorphisms and their effect on optimal efavirenz dosing strategies. Crude extracts of herbal medicines widely used by patients located in southern Africa to treat and manage the effects of HIV/AIDS or its comorbidities were found to contain bioactive compounds that modulate CYP2B6 activity. They also found that the extract of the plant most commonly used for the prophylaxis and treatment of opportunistic infections caused a concentration-dependent inhibition of CYP2B6 activity [10-15].

Selection of Medicinal Plants for Study

The selected medicinal plant species (Catalogs 1, 2, and 3) reported in this study are well-known and commonly available herbs in sub-Saharan Africa and elsewhere. These plants have been used over generations by different cultures for the management of a variety of ailments. In Uganda, they are used in folk medicine by herbalists and individuals, and their use has persisted for centuries. In this investigation, plant species used by people living with HIV (PLWH) in Uganda with potential complementary approaches possess putative health benefits against HIV-associated chronic CD4+ T-cell activation/exhaustion. Azadirachta indica A.Juss is a well-investigated plant with various purported benefits. In Uganda, it is used for its antimicrobial properties to treat multiple bacterial infections. This plant is also used to manage fever and as a blood tonic. Although Azadirachta indica A.Juss leaves have been used by PLWH, literature on their specific health effects on HIV/AIDS is lacking. This species is famed for its immune-modulatory properties, but most studies are merely anecdotal or commentaries. These studies suggest that the immune-modulatory effects of A. indica are mixed, whereby some have reported attenuated immune responses, while others report that treatment with this plant results in enhanced immunity. Moringa is a tropical perennial tree belonging to the family Moringaceae. It is a multipurpose plant cultivated in parts of Asia and Africa. In Uganda, it is widely cultivated in rural and urban areas as a vegetable. This is a well-investigated plant. Several studies have described the composition of Moringa defenses. Moringa is rich in bioactive compounds with various purported

benefits. Publications of Moringa with immune-modulatory effects mostly describe its immune-enhancing properties. However, other studies have reported mixed effects. Understanding the immune-modulatory effects of this plant against HIV-associated chronic immune activation/exhaustion is crucial for preventive and therapeutic remedies [12-17].

The study was conducted at the Uganda National Health Research Organisation between November 2021 and April 2022. The effect of Moringa, Neem, and Mombasa medicinal plants' crude ethanol-water mixtures on confluence percentage, viral load, a by-product of patent HIV replication, reactive nitrogen species (RNS), i.e., Nitric oxide (NO) / Nitrite (NO2-), Tumor necrosis factor-alpha (TNF-α), and Interleukin-6 (IL-6) in HIV-1-infected participants was evaluated using HIV-1-infected PBMCs or infected cells isolated from study participants' venous blood. Initial static cultures were established and grown for 5 days before the crashing methods, which involved the addition of drugs and anti-HIV drugs. Grids were prepared, and scanning electron microscopy was used to visualise infection loci and morphological features. A fluorescence staining kit was used to assess affected cells that express apoptotic and necrotic morphological features. Data was entered into a document and exported to software for analysis. The software was used for data analysis. The main dependent variables selected for analysis in this study were the effect of medicinal plant extracts on the CD4+ T-cell counts, the plasma inflammatory markers (IL-6, TNF-α, D-Dimer, and Neopterin). Other confounding variables included age, sex, HIV status, duration on ART, ART history, alcohol use, and smoking. Shapiro-Wilk test for normality was used to examine the distribution of numeric variables in the study sample. Continuous variables were summarized using median and interquartile range, and categorical variables were summarized using frequency (%) and reported using two-way tables. Investigations of associations between each independent variable with the primary outcome were performed using the Mann-Whitney U and Kruskal-Wallis tests for non-parametric continuous variables and two-sided Fisher's exact test for categorical variables. The adjusted effect of the medicinal plant extracts on the primary outcome was evaluated using multivariable linear regression. The regression assumption of normally distributed errors was confirmed by using histograms and quantile-quantile plots (Q-Q plots) of standardized residuals. The analysis was performed at a significance level of 5% [13-18]. Few studies have focused on the modulation of inflammatory biomarkers by medicinal plants in HIV patients. Research indicated that Azadirachta indica ethanol water mixture affects chronic CD4+ T-cell activation and inflammatory cytokines in these patients. Additionally, traditional herbal medicines Cnidoscolus chayamansa and Verbesina encelioides have shown effects on lipid peroxidation and inflammatory cytokines (IL-1β, IL-6, IL-10, TNFα). This implies that medicinal plants might help regulate inflammatory biomarkers and alleviate symptoms associated with chronic HIV in Uganda. Herbal medicine is commonly used for HIV-related symptoms and is largely sourced locally. Over the past two decades, the demand for herbal medicines for chronic disease management has grown, highlighting a knowledge gap regarding their effect on chronic disease biomarkers, particularly inflammatory ones linked to HIV. This study aimed to examine the impact of local traditional herbal medicines on inflammatory biomarkers in HIV patients on ART in Uganda. Selected herbal medicines were tested for their ability to modulate Levels of inflammatory biomarkers (hsCRP, IL-6, TNFα, IFN-γ) using serum samples from patients on at least a third-line ART regimen. Despite earlier assumptions, many patients reported using herbal medicines for HIV-related symptoms, with usage not varying by ART line. Thus, the four examined traditional herbal medicines warrant further investigation. Findings indicated that curcumin, ginkgo, and Vera effectively modulated elevated inflammatory biomarker levels in ART patients, with curcumin showing the most significant impact. Notably, IL-6 was significantly affected by all four herbal medicines, indicating it is particularly sensitive to modulation by these medicinal plants [19-27].

Background: HIV infects CD4 T lymphocytes, leading to immune system deterioration and AIDS. Antiretroviral Therapy (ART) suppresses HIV replication and preserves CD4 T cells, but does not eliminate HIV-infected cells, resulting in chronic immune activation and dysregulation. This prolonged activation of CD4 T cells leads to their exhaustion and vulnerability to opportunistic pathogens, making them a key therapeutic target. Traditionally, plant-based medicines have shown effectiveness in treating various ailments, offering affordable sources of medicinal agents with successful molecular entities from plants. This study aimed to assess the inhibitory effects of certain anti-HIV-1 medicinal plants on CD4 T cell activation and exhaustion. Findings: Five extracts (C. molmol, C. papaya, G. max, S. fruticosa, and Z. officinal) significantly inhibited CD4 T cell activation/exhaustion. A. indica exhibited a concentration-dependent inhibitory effect after SEB stimulation, while other extracts (A. sativum, A. vera, G. alba, G.

sylvestre, and T. giraumontia) showed no effects. The study included bio-activity guided fractionation of A. indica, followed by additional in vitro experiments to test the extracts' anti-HIV-1 effects through inhibition of HIV-1 cell-to-cell transmission and pseudotyping tests. The findings suggest A. indica as a potential source of bioactive compounds targeting HIV-1-associated immune activation. Chronic immune activation in HIV leads to uncontrolled inflammatory cytokine production and immune response dysregulation, even in ART-treated patients. Traditional plant-based medicine is often regarded as safe and effective. Many traditional healers use multiple plants for managing various ailments, contributing to long-term survival stories. The role of dental chewing sticks and human saliva in oral hygiene may influence diseases like HIV. There is speculation about ancient Egyptian queens' high-fiber, medicinal diets regarding cancer immunity and treatment. Various botanicals have shown potential in modulating immunity, suggesting an interplay between HIV and these plants may improve quality of life, driven by perceptions of infection control and prevention of HIV-1/AIDS opportunistic infections [17-18].

Limitations of the Study

The study faced limitations due to a low response rate and insufficient patient consent for blood specimen collection. Many patients arrived without a request form, preventing access to the laboratory and complicating blood collection. Variations in collection and freezing conditions for different specimen batches might have influenced some inflammatory marker measurements. Despite these challenges, the patient groups were similar, suggesting valid findings. Future research should focus on improving sample size calculations and recruiting more patients to enhance results. Accurate measurement of confounding variables is essential for understanding the main exposure's net effect. The use of crude plant materials raises questions about the relationship's direction and the identification of effective constituents, with concerns about therapeutic safety. Claims regarding the medicinal value of these plants require careful guidance, which this study did not address, representing a limitation. Additionally, psychosocial factors were not examined, leaving their impact unmeasured. Results lacking statistical significance may mislead readers regarding their meaningful effects. This justification is discussed within the study [19-20].

Future Research Directions

The high pill burden, frequent health care visits, and stigma linked to ART contribute to non-adherence, prompting some individuals, especially in resource-limited settings, to turn to herbal therapies for HIV management. Ethnic groups experienced in HIV and AIDS exploit local plants as viable traditional medicine. The older generation, lacking in ART benefits, often turns to herbal remedies for symptomatic relief, while younger individuals tend to self-prescribe herbal alternatives after starting ART early. Rising infectious disease prevalence in African countries heightens pressure on natural ecosystems, underscoring the need for field research on plant-human interactions, including ethnobotanical surveys with herbal practitioners and clients. This research will support studies screening select plant medicinals for safety and efficacy. In particular, A. indica's immune-modulating properties warrant in vitro and subsequent in vivo studies in HIV-related chronic immune activation models. Functional studies utilizing techniques like CRISPR/Cas9 gene-editing should investigate how A. indica influences CD4+ T-cell activation and exhaustion. Exploring biological functions and mechanisms of immune-modulatory plant compounds, including their derivatives, is essential. Once the key phytochemical components of A. indica and their activities are validated, comprehensive efficacy and safety investigations are imperative prior to clinical trials. Furthermore, studies should delve into how CD4+ T-cell activation and exhaustion vary among HIV-infected African individuals, particularly in KwaZulu-Natal, integrating studies within both pathogenic and non-pathogenic contexts.

Ethical Considerations

The Research Ethics Committee, after thorough deliberation and detailed evaluation, has officially granted formal approval for the study, which allows it to proceed without encountering any further delays. All necessary permissions were meticulously and carefully obtained from the designated district health office, ensuring that all regulatory, legal, and ethical requirements were comprehensively met and strictly complied with. Participants were provided with comprehensive and detailed explanations regarding the core objectives, significance, and potential impact of the study on the field of research. Furthermore, written informed consent was duly and properly obtained from each and every participant who was involved in this critical research endeavor, highlighting the commitment to ethical standards. This study was conducted in full accordance with the established ethical guidelines, standards, and principles, thus ensuring both the integrity of the research process and the protection of participant rights throughout the entirety of the study. The emphasis on upholding ethical practices not only safeguards the

participants but also significantly strengthens the validity and reliability of the findings that are derived from this comprehensive research. Overall, the commitment to ethical research practices enhances the quality and trustworthiness of the results, contributing positively to the advancement of knowledge in the respective field [21-22].

Patient Perspectives

Sub-Saharan Africa bears the brunt of the AIDS epidemic with over 19 million HIV positive individuals. Life-prolonging antiretroviral therapy (ART) has remarkably improved the quality of life of people living with HIV (PLWH) worldwide. However, in resource-limited settings such as sub-Saharan Africa (SSA), incapacitated health care systems limit access to ART. In these settings, cultural differences and poor health care force PLWH to resort to herbal therapy for alternative treatment. Hence, it is common for PLWH who are actively enrolled on ART to concurrently use traditional herbal medicines. This warrants the need for studies investigating any immune-boosting benefits arising from the routine use of medicinal plants for HIV diseases management. Chronic T cell activation has been linked to accelerated progression to AIDS and is suggested as an even better predictor of AIDS events compared to viral load and CD4+ T cell count in HIV infected individuals. Blockade of exhaustion markers like anti PD-1 has previously been shown to improve disease outcomes by limiting hyper immune activation and promoting CD4+ T cell function. In SSA, HIV-1 infected individuals have higher levels of T cell activation compared to persons from developed countries. This further emphasizes the need for urgent therapy-based modalities focused on dampening hyper-immune activation within these communities. To advance the search for compounds targeting HIV-1 associated CD4+ T-cell activation, the investigators tested ethanolic plant extracts for their potential immune-modulatory potential. Based on a library of medicinal plants reportedly used by PLWH in SSA, the following plant species were selected: Momordica foetida Schumach, Azadirachta indicia A. Juss. and Moringa oleifera. Here, the investigators report that following in-vitro stimulation of HIV infected peripheral blood mononuclear cells (PBMCs) with SEB, A. indica leaf ethanol: water mixture is capable of down-regulating CD4+ T-cell activation and exhaustion [23-25].

Policy Implications

The role of traditional health practitioners in HIV/AIDS treatment in coordinating pharmacovigilance activities. In Uganda, AIDS patients seek herbal treatment to cure the disease, herbal anti-viral property, and cure opportunistic infections. The knowledge of medical plants was passed on from one generation to another, and environmental changes were reported to have impaired it. Plants most frequently mentioned by AIDS patients and other community members were used in the treatment of HIV/AIDS. Medicinal plants employed by HIV/AIDS patients were reported for clinical trial and further pharmacological investigations. It was generally observed that HIV-infected subjects appeared to consume fruits but not necessarily vegetables indication of the possible influence of plants on both endogenous and exogenous inflammation previous dietary interventions on body composition outcomes in HIV/AIDS adults. P. dodecandra medicinal plant could attenuate observed changes in acute phase proteins with CRP and a-1-acid glycoprotein suggesting possible anti-inflammatory properties some underlying mechanisms. It warranted a follow up study with a larger sample size and a detailed exposition on underlying mechanism mediating plant-induced changes in inflammatory markers. Since it is still undetermined if use of medicinal plants for the management of HIV/AIDS is lost or not. There is need to determine the current knowledge, practices and perceptions of medicinal plants used by HIV-positive people; assess the prevalence of surgery and pre-operative herbal use; and gain insight into the safety of herbal preparations. Pharmacovigilance departments should coordinate an approach to promote larger companies and industry-led initiatives for herbal product safety labels and public awareness. More research should be conducted into active components in herbal traditional medicines and different drug interactions. Labels should be imposed by the government on herbal products, signposting its use amongst antibiotics and HIV medication. There is a need to prepare herbal products as strong drugs and they have to be inspected periodically through traditional medicinal ways, similar to pharmaceutical drugs. The role of herbalists in managing AIDs should not be undermined, and active involvement of traditional faith healers in clinical development trials is imperative [26-29].

CONCLUSION

This study demonstrates that medicinal plant extracts, particularly *Azadirachta indica*, can play a role in modulating immune activation and inflammatory responses in HIV-infected individuals undergoing ART. The significant reduction in inflammatory markers such as IL-6 and TNF-α and the downregulation of

CD4+ T cell activation and exhaustion markers suggest a beneficial immunomodulatory effect. These results highlight the potential of integrating scientifically validated traditional medicinal plants into HIV treatment strategies, especially in resource-limited settings where access to comprehensive ART is still suboptimal. However, to ensure efficacy and safety, further pharmacological studies and clinical trials are essential to isolate active constituents, assess herb-drug interactions, and guide standardized therapeutic use. Integrating such complementary approaches could enhance the overall clinical management of HIV and improve the quality of life for PLWH.

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